REMARKS

Claims 1, 3-5 and 11-15 are pending in the application, of which claim 1 is being amended.

Claim 1 is being amended without any rejection of said claim language by the Examiner, only for cosmetic reasons, namely, to recite a method for the pulmonary administration of a dry powder drug composition from a passive dry powder inhaler to the respiratory tract of a patient. This claim language is supported by the Specification at page 7, lines 1-3. The claim amendments add no new matter, and consequently, their entry is respectfully requested.

103(a) Rejection

The Office Action rejected claims 1, 3-5 and 11-15 under 35 U.S.C. 103(a) as unpatentable over Edwards et al., in view of Vaghefi.

Applicant respectfully traverses the rejection. Claim 1 and the claims dependent therefrom, are patentable under 35 U.S.C. 103(a) over Edwards et al. in view of Vaghefi, because the cited combination does not establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness under 35 U.S.C. 103:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

1. The Office Action Does Not Consider the Claimed Invention As a Whole.

To establish obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983).

Neither Edwards et al. nor Vaghefi teach claim 1, which is to a method for the pulmonary administration of a dry powder drug composition from a passive dry powder inhaler to the respiratory tract of a patient, comprising, inter alia, providing a dry powder drug composition comprising particles comprising a lipid matrix and a particle size of 1-30 microns, mass median aerodynamic diameter of less than 5 microns, and bulk density of less than $0.5g/cm^3$; loading the drug composition into a passive dry powder inhaler having a resistance of from 0.01 to 0.30 $(cmH_20)^{1/2}/Lmin^{-1}$; and administering the drug composition from the inhaler to the respiratory tract of a patient, wherein the emitted dose is at least 60% for flow rates from 10 to 60 liters per minute.

Edwards et al. does not teach claim 1 and instead generally teaches the preparation of particles that incorporate a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system. (Abstract) Edward et. al.'s teachings to the preparation of such particles are not teachings to the claimed method of adminstering a dry powder drug. Specifically, the Office Action ignores the claimed steps of loading the claimed composition into a passive dry powder inhaler having a resistance of from 0.01 to 0.30 $(cmH_20)^{1/2}/Lmin^{-1}$. Edwards et al. also does not teach the claimed step of adminstering the drug powder composition with an emitted dose that is at least 60% for flow rates from 10 to 60 liters per minute. Thus, the Office

Action is not considering all the words of claim in judging the patentability of the claim 1 against Edwards et al..

Vaghefi does not make up for the deficiencies of Edwards et al. because Vaghefi does not teach providing a dry powder drug composition having particles comprising a lipid matrix, a particle size of 1-30 microns, mass median aerodynamic diameter of less than 5 microns, and bulk density of less than 0.5g/cm^3 as claimed. Nor does Vaghefi teach the step of loading the claimed dry powder composition into a passive dry powder inhaler having a resistance of from 0.01 to 0.30 $(cmH_20)^{1/2}/Lmin^{-1}$. Vaghefi also does not teach obtaining administration of the drug powder composition from the inhaler to the respiratory tract of a patient provide an emitted dose that is at least 60% for flow rates from 10 to 60 liters per minute. Vaghefi generally teaches the structure of a dry powder inhaler but does teach any of the steps of the claimed dry powder administration method.

Thus the Office Action is disregard the words of claim 1, and is not considering the claim as a whole. When claim 1 is considered as a whole, it is clear that a prima facie case of obviousness over Edwards et al. in view of Vaghefi has not been established by the Office Action, since neither reference teaches the claimed language.

2. <u>There Is No Motivation to Combine the References in the Manner Suggested By the Office Action</u>.

To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Second, there must also be a reasonable expectation of success for such a combination. Third, the prior art references that are combined must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

The Office Action has not demonstrated that there is any motivation to combine the teachings of Vaghefi into the teachings of Edwards et al. to meet the claim limitations. Edwards et al. does not teach the claimed dry powder administration method which produces a consistent emitted dose of at least 60% for widely variable flow rates of 10 to 60 liters per minute. Nor does Edwards et al. teach that such a method can be achieved for a wide range of resistances of passive dry powder inhalers ranging from 0.01 to 0.30 $(cmH_20)^{1/2}/Lmin^{-1}$. Instead, Edwards et al. generally teaches preparation of particles that have a surfactant and hydrophilic or hydrophobic complexes. Edward et al. does not teach that such particles can provide a drug administration method which achieves consistent emitted dose for a wide range of passive dry powder inhaler resistances and flow rates.

Furthermore, there is no motivation to combine the teachings of Vaghefi into Edwards et al. to derive the claimed invention. Vaghefi does not teach a method of inhalation which uses a dry powder drug composition having the claimed particle limitations, namely that the particles comprise a lipid matrix and a particle size of 1-30 microns, mass median aerodynamic diameter of less than 5 microns, and bulk density of less than $0.5g/cm^3$. Nor does Vaghefi teach that such particles can achieve the claimed consistent emitted dosages over a wide range of dry powder inhaler resistance and flow rates. Vaghefi generally teaches the structure of a dry powder inhaler but does not motivate derivation of the claimed dry powder inhalation method which used particular types of particles to achieve unexpected results.

The Office Action does not explain why one of ordinary skill would be motivated to select particular dry powders having the claimed characteristics from the generalized teachings of Edwards and then apply these dry powders to the dry powder inhalers of Vaghefi to derive the claimed invention. There is no teaching or suggestion in Vaghefi that particular dry powders, or the ones taught by Edwards et al., will provide a reasonable expectation of consistent emitted dosages over a wide range of inhaler resistances and flow rates. Nor does Edwards et al. teach that low variability results

can be achieved with the particular dry powders. The Office Action has not explained why the suggested combination of these references will produce the successful outcome recited in claim 1.

It should be further noted that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, Ibid. It would appear that the Office Action is relying on Applicant's disclosure to find an expectation of success from the cited references.

The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The experimentation required to derive a dry powder administration method having the claimed particle limitations to achieve consistent emitted dosages for a variety of inhaler resistances and flow rates, by selecting particles from the numerous different types of particles taught by Edwards et al. and individually testing the particles in a variety of inhalers, is substantially experimentation. Neither reference motivates one of ordinary skill in the art to perform such substantial experimentation. Nor do the cited references teach one of ordinary skill in the art to select a particular type of particle from Edwards et al. and apply the same to an inhaler taught by Vaghefi. Such a reconstruction of the invention can only be in hindsight, absent motivation in the cited references that teach or suggest the claimed combination. The Office Action should view the cited references without the benefit of the impermissible hindsight vision afforded by the claimed invention. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Thus, there is no motivation to combine the teachings of Vaghefi into the teachings of Edwards et al., to derive the claimed method for administering a dry powder composition to a patient

3. The Unexpected Results of the Claimed Method Negate a Finding of Obviousness.

Moreover, it is not obvious that any one of the possible combinations of the Edwards et al. particles and the Vaghefi inhalers would produce the unexpected results of the claimed method. The unexpected results of the claimed invention cannot be derived in hindsight using an "obvious to try" rationale based on hundreds of possibilities and combinations. One might extrapolate this argument to render unpatentable all methods of delivering dry powder formulations of a pharmaceutical compound simply because a spray dried particles are known or because methods of dry powder inhalation are known. Unexpected results negate such a finding of obviousness.

As explained in the Specification, the claimed administration method provides such surprising and unexpected benefits to negate a finding of obviousness. The claimed method solves problems in the inhalation of dry powder compositions from passive dry powder devices. Passive dry powder devices are desirable because aerosol generation and inhalation are properly synchronized since the patient provides the energy needed to aerosolize the dry powder formulation by their own inhalation. Synchronization maximizes dose delivery of the dry powder compositions to the lungs. However, the air flow rate through the passive device can vary drastically between individual patients or for different inspiration efforts by the same patient. The variable air flow rate is also governed by the inherent resistance of the device. As a result of these variables, the emitted dosage often varies from one patient to another and between different inspirations by the same patient. Emitted dosage is also dependent on the ability of the dry powder composition to be dispersed within a gas stream, the air flow rate to deagglomerate a powdered formulation, and the aerosolized formulation to adequately reach the deep lung. (Background of the Invention, first paragraph, page 2). Reductions in the flow rate dependence and dosage variability, are especially important for drugs which have a narrow therapeutic index for which the dose of drug must be

accurately controlled (e.g. insulin for a diabetic patient.) (Specification, page 7 lines, 7-10.)

Applicant has discovered a surprising and unexpected benefit that consistent emitted doses that are substantially independent of the inhalation flow rate of a patient can be obtained by aerosolization of the claimed particles in a passive dry powder inhaler. Applicant has discovered that particles comprising a lipid matrix, a particle size of 1-30 microns, mass median aerodynamic diameter of less than 5 microns, and bulk density of less than 0.5g/cm^3 when loaded in a claimed passive dry powder device having the claimed resistance levels provide a more consistent emitted dose of at least 60% for a wide variety of flow rates that can range from 10 to 60 liters per minute. This unexpected and surprising result is not taught or suggested by Edwards et al. or Vaghefi and consequently, negates a finding of obviousness.

The surprising results of the claimed invention are demonstrated in the examples provided in the Specification. For example, in Example 1, the consistency of emitted dose, which is dependent on the aerosol characteristics of the claimed dry powder formulation, was examined in several different passive inhaler devices. These commercially available devices had a wide range of resistances ranging from 0.04 (Glaxo Rotohaler) to 0.2 (Flowcaps). It was expected that the wide range of resistances of the inhalers would produce an equivalently wide range of emitted dose. However, it was determined that both devices having high resistances and those with low resistances were able to effectively disperse the dry powder composition, independently of the inspiration flow rate. (Specification, page 19 line 23 to page 20.) Another surprising result is that the interpatient variability in lung deposition, as shown in Table 3 on page 22, was also significantly reduced at values of 11–13% RSD for inhalation using the claimed dry powder composition and inhaler, versus 22-34% RSD for inhalation using a commercially available inhaler (Pulmicort Turbuhaler.) As yet another example, interpatient variability was also found to be significantly reduced for the claimed dry powder adminstration method as compared to inhalation using a nebulizer, as demonstrated in Table 6 on page 24 of the Specification. Table 6 demonstrates that

a nebulizer dry powder composition provides an interpatient variability in lung deposition of 40%, versus the claimed method produced an interpatient variability of 17%, which is 50% lower. These unexpected and surprising results negate a finding of obviousness.

Neither Edwards et al. nor Vaghefi teach or suggest a method for delivering a dry powder composition to a patient's respiratory tract in which the composition and inhaler provide consistent emitted doses are independent of the resistance of the inhaler and also produce low interpatient variability. Edwards et al. teaches dry powder preparation but do not teach an inhalation method producing the claimed functional results. Vaghefi teaches inhalation devices, but does not teach the claimed dry powder composition or that such a composition can produce an unexpected low variability in emitted dose for different dry powder inhalers.

For these reasons, claim 1 and the claims dependent therefrom are not obvious over Edwards et al. and Vaghefi.

CONCLUSION

The above-discussed amendments are believed to place the present application in condition for allowance. Should the Office Action have any questions regarding the above remarks, the Office Action is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,
JANAH & ASSOCIATES, P.C.

Date: November 18, 2005

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